

論文の内容の要旨

Analyses of histone modification reprogramming and establishment of in vivo epigenome editing in medaka embryos

(メダカ受精卵におけるヒストン修飾のリプログラミング動態解析
と in vivo エピゲノム編集技術の確立)

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In the last century, DNA sequence alone was regarded as the molecular entity of phenotypic inheritance. However, this view has been challenged by the findings of DNA sequence-independent inheritance in many species. Now, it is widely accepted that parental exposure to environmental stimuli, such as nutrient stress, physical stress, and chemical exposure, can affect traits in offspring, probably via inheritance of epigenetic modifications such as DNA methylation and histone modification from parental germ cells to offspring. However, compared to DNA methylation, it is not yet well characterized whether histone modifications can be inherited intergenerationally. This is due to the limited number of species in which their dynamics of histone-modification resetting after fertilization has been well studied, and also due to the lack of technology with which to assess the causality between epigenetic changes in germ cells and embryos.

In this doctoral thesis, I took advantages of Japanese killifish, medaka (*Oryzias latipes*), and sought to solve these problems. In Chapter 1, to reveal epigenetic reprogramming of histone modifications in medaka early development, I analyzed histone modification

patterns after fertilization, genome-widely and quantitatively. As a result, the extensive erasure of histone modifications is further supported as conserved reprogramming mode among non-mammalian vertebrates. Furthermore, my study found retention of some modification during reprogramming and identified genetic and epigenetic characters, suggesting mechanisms and biological roles of pre-marking of those modifications, and possibility of intergenerational inheritance of such modifications. In Chapter 2, toward the future direct test of the inheritance of histone modifications, I established a technology of site-specific and *in vivo* histone modifications, or *in vivo* epigenome editing, in medaka embryo. My study will further help to understand the dynamics of epigenetic reprogramming among many species and to explore the possibility of intergenerational inheritance of histone modification in non-mammalian vertebrates.